

polymer film or polymer gel pad, and a different immobilized oligonucleotide probe; b) a voltage source connected to the microelectrodes; c) an electrolyte solution comprising a solution of  $\text{Li}^+$  ions; and d) a detector connected to the microelectrodes.  $\text{Li}^+$  is chosen in the electrolyte solution because its small size facilitates intercalation of  $\text{Li}^+$  cations into the nucleic acid duplex, and has less diffusion resistance. See lines 29, page 13, to lines 2, page 14 of the specification.

Heller discloses a microelectronic device designed to control and actively carry out a variety of assays and reactions at an array of micro-locations. Each micro-location comprises an attachment layer, a permeation layer, and an underlying direct current micro-electrode. Because the device can actively concentrate analytes and reactants, the device facilitates detection by fluorescent and optical detection. See, for example, col. 19, lines 21-42.

Wiles teaches an electrochemical reference element having a metal electrode such as silver coated with the tetraphenyl salt of the metal. The element may form the internal reference of an ion selective electrode with an ion selective membrane carried directly upon the TPB coating. The element provides a thermodynamically reversible couple suitable for use in a non-aqueous environment.

As the Examiner is aware, the test for obviousness is whether the claimed invention as a whole would have been obvious at the time it was made to a person of ordinary skill in the art. A *prima facie* case of obviousness requires three elements: (1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. See M.P.E.P. § 2142.

Applicants respectfully submit that there is no motivation to combine the teachings in the references to come up with the present invention, i.e., neither Heller nor Wiles teaches or suggests the use of an electrolyte solution comprising a solution of  $\text{Li}^+$  ions in an electronic device for molecular interactions.

The Examiner referred to the last paragraph on column 4 of Wiles as an indication of motivation to combine. This paragraph states:

"Ammonium, sodium, hydrogen, *lithium*, calcium, magnesium, nitrate, chloride, phosphate and other inorganic cation and anion selective electrodes may be constructed by coating the appropriate permselective membrane on to the Ag/AgTPB electrodes. In a similar fashion...[e]lectrodes based on the binding of proteins, DNA, RNA, viruses and cells to an

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affinity ligand incorporated into the appropriate membrane may *also* advantageously use the Ag/Ag-TPB electrode.”

Applicants submit that this paragraph merely elaborates the different possibilities of using the inventive reference element in Wiles. That is, the reference element can be used for the construction of a lithium electrode. As an alternative, the reference element can *also* be used for the construction of electrodes “based on the binding of proteins, DNA, RNA....” Nowhere in this paragraph teaches or suggests that a lithium-based buffer can be used *in combination* with an electronic device for molecular interactions. Therefore, Applicants respectfully submit that Wiles does not teach or suggest a motivation to combine.

Furthermore, there is no reasonable expectation of success by combining the teachings of the references. As we stated in our previous response, the combination of Heller and Wiles may have, at most, resulted in the use of a lithium electrode in Heller’s device. There is no reasonable expectation that the Li<sup>+</sup> ion in the resulted device will be able to advantageously facilitate the electrical detection of nucleic acids.

Accordingly, Applicants respectfully submit that a prima facie case of obviousness has not been established for claims 36-55, and request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

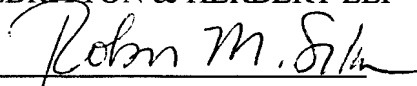
### CONCLUSION

In view of the foregoing, Applicants respectfully submit that claims 36-55 are in a condition for immediate allowance. Therefore, issuance of a formal notice of Allowance at an early date is requested.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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